Infections, rheumatisms and autoimmunity

Infections, Rheumatisms and Autoimmunity, March 6–8 2008, Milan, Italy

Gianfranco Ferraccioli
Catholic University of the Sacred Heart, Department of Rheumatology, School of Medicine, Rome, Italy
Tel.: +39 063 503 654; Fax: +39 063 503 523; gf.ferraccioli@rm.unicatt.it

Autoimmune chronic inflammatory diseases are thought to have a prevalence of one in 30 people in the Western world. Understanding how environmental factors can eventually lead to such a burden is of crucial importance. In a recent meeting held in Milan, Italy, the cellular and molecular basis of autoimmunity arising following infection, and protection against autoimmunity induced by infection, were discussed by more than 100 scientists from around the world.

Innate immune response

In the first session of the meeting, a comprehensive update regarding how infectious agents interact with cells of the immune system was made. A Cook (University of Cambridge, UK), MH Claesson (University of Copenhagen, Denmark), T Avcin (University of Ljubljana, Slovenia) and HJ Girshick (University of Wuerzburg, Germany) discussed small, structurally conserved molecules (pathogen-associated molecular patterns), which are recognized to play a fundamental role in the early recognition of several infectious agents (e.g., Gram-positive and Gram-negative bacteria and RNA or DNA viruses) by the immune system. These molecules (bacterial cell-surface lipopolysaccharides, lipoproteins, lipopeptides, liporabinomannan, proteins such as flagellin from bacterial flagella, viral dsRNA, the unmethylated CpG islands of bacterial and viral DNA, and certain other RNAs and DNAs) are sensed by Toll-like receptors (TLRs) [1,2], a type of pattern-recognition receptor. They belong to the same receptor superfamily as the IL-1 receptors (IL-1 TLR superfamily), which all have the so-called Toll-IL-1 receptor (TIR) domain. There are three TIR-domain subgroups: group 1 are receptors of interleukins and have extracellular immunoglobulin domains; group 2 are TLRs and directly or indirectly bind pathogen-associated molecular patterns; and group 3 are cytosolic adaptor proteins whose role is to transmit signals from proteins of groups 1 and 2. Some TLRs seem to rely mainly on MyD88 to produce cytokines, such as IL-6 and TNF-α, while others rely on adaptor molecules and transcription factors, such as TIR-domain-containing adapter-inducing IFN-β, TNF receptor-associated factor 6, IL-1 receptor-associated kinase-1, and IFN regulatory factor-7.

H Amital (Tel Aviv University, Israel) and AL Zignego (University of Florence, Italy) focused on the issue of infectious agents (cytomegalovirus, Helicobacter pylori, hepatitis B virus [HBV] and hepatitis C virus) and innate immune response. At least 11 TLRs are recognized in humans, and among these, TLR3, TLR7, TLR8 and TLR9 are expressed intracellularly within one or more endosomal compartments. TLR3 shows specificity for polyinosinic-polycytidylic acid compounds and dsRNA, TLR7 and TLR8 recognize imidazoquinolines and ssRNA, and TLR9 binds dsDNA. In a normal immune response, these TLRs should induce an antipathogen immune response while avoiding the induction of autoimmune diseases. This means that the key functional outcome of TLR ligation is the production of an inflammatory response through transcription factors, such as NF-κB. Of the TLRs, the DNA- and RNA-binding members have been shown to lead to the production of large amounts of IFN-α, mostly derived from plasmacytoid dendritic cells. This cytokine is of special interest to investigators studying autoimmune systemic lupus erythematosus (SLE) or Sjogren’s syndrome because its expression has been correlated with disease severity in some studies. In summary, the inflammatory response downstream of TLR ligation is mainly characterized by an inflammatory milieu comprising IL-6, TNF-α and IFN-α, which represents an optimal combination for inducing immune cells to clear an infectious agent, and also the most appropriate setting to favor autoreactive B-cell clonal expansion. In addition, several studies have shown that endogenous mammalian ligands of TLR7, such as small ribonucleoproteins, are capable of stimulating B cells and plasmacytoid dendritic cells. Interestingly, it was recently reported that TLR7 ligands induce higher IFN-α production in females.

Models of innate immune response & autoimmune diseases

L Guillevin (University of Paris Descartes, France) and CGM Kallemberg (University of Groningen, The Netherlands) focused their discussion on the role of infectious agents in autoimmune vasculitic diseases. In animal models of lupus nephritis, some TLRs (TLR3 and TLR9) are specifically immunolocalized in the kidneys, suggesting a possible pathogenetic role in the manifestation of the disease [3]. Experimental evidence shows that MRL/lpr mice that spontaneously develop proliferative glomerulonephritis in the context of an SLE-like
In chronic HBV infections, supernatants from TLR3- and TLR4-stimulated Kupffer cells and TLR3-stimulated sinusoidal endothelial cells from wild-type mice were able to potently suppress HBV replication. Using neutralizing antibodies, we demonstrated that the TLR3-mediated, but not the TLR4-mediated, effect is exerted exclusively through IFN-β. This could have implications for the development of TLR-based therapeutic approaches against HBV [8].

Conclusion

All these data have led investigators to believe that understanding the molecular events leading to T-cell, B-cell, monocyte/macrophage and dendritic cell activation will help to devise new therapeutic strategies to control the inflammatory events that occur in autoimmune diseases and develop new therapies that target key molecules or signals involved in the different phases of these diseases [10]. Of particular interest is the counter-regulation that occurs during simultaneous stimulation of TLR7 and TLR9 on human plasmacytoid dendritic cells and B cells. Interestingly, it has been observed that the capacity for potent IFN-α induction by TLR9 ligands such as CpG-C and CpG-A is markedly reduced by concurrent small-molecule TLR7 stimulation [9].

Future perspective

Ligands of TLR7, and other modalities to control innate immune activation, could be employed to downregulate TLR9 activation in B cells and autoantibody synthesis.

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.
Executive summary

- More and more evidence of a strict coupling between innate immunity and development of autoimmunity has been uncovered by recent investigations and by in vivo studies in humans.

- A full molecular understanding of the various signals occurring in the different cell populations of the immune system will allow investigators to devise new methods to control innate immune activation and autoimmunity occurring downstream of innate immunity activation.

- Innate immunity-related receptors and signaling molecules could become therapeutic targets to stop autoimmunity.

Bibliography


Affiliation

- Gianfranco Ferraccioli
  Catholic University of the Sacred Heart, Department of Rheumatology, School of Medicine, Rome, Italy
  Tel.: +39 063 503 654
  Fax: +39 063 503 523
  gf.ferraccioli@rm.unicatt.it